TRANSLATION

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Name of Document;	Claims	1
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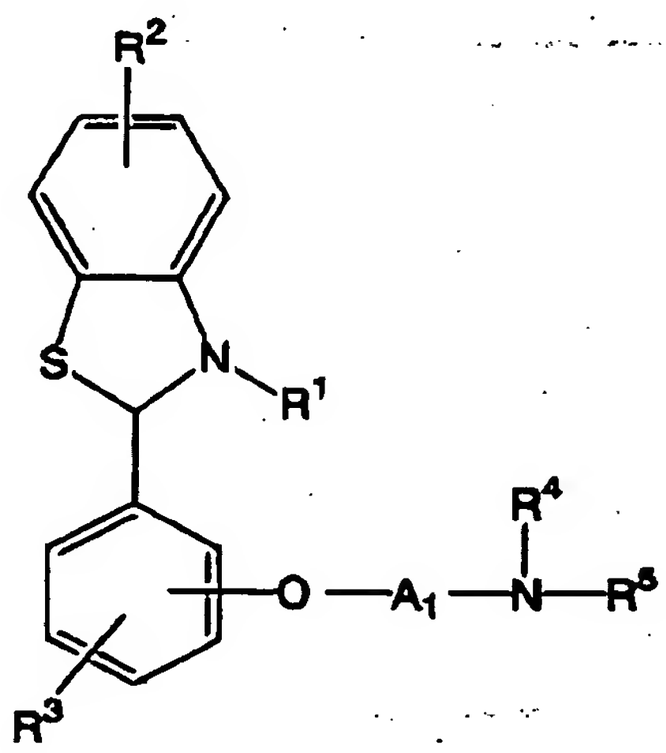
NAME OF THE DOCUMENT

CLAIMS

1. An inhibitor of pain threshold decrease comprising a κ-opioid receptor agonist as an active ingredient.

2. The inhibitor of pain threshold decrease as claimed in claim 1, characterized in that it is applied to treatment of chronic pain.

3. The inhibitor of pain threshold decrease as claimed in claim 1 or 2, wherein the κ-opioid receptor agonist is a compound represented by the following general formula or a salt thereof.



wherein R^1 represents an acyl group;

R^2 and R^3, which are the same or different, represent a

hydrogen atom, a halogen atom, an alkyl group, a cycloalkyl group, an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, a carboxy group or its ester, an alkylcarbonyl group, an arylcarbonyl group, an amino group, an alkylamino group, an arylamino group, a cyano group or a nitro group, the alkyl group, the cycloalkyl group, the aryl group, the alkoxy group, the aryloxy group, the alkylcarbonyl group, the arylcarbonyl group, the alkylamino group or the arylamino group can be substituted with a halogen atom, an alkyl group, a cycloalkyl group, an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, a carboxy group or its ester, an alkylcarbonyl group, an arylcarbonyl group, an amino group, an alkylamino group, an arylamino group, a cyano group or a nitro group;

R^4 and R^5, which are the same or different, represent a hydrogen atom, an alkyl group, a cycloalkyl group, an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group or an acyl group, the alkyl group, the cycloalkyl group, the aryl group, the alkoxy group, the aryloxy group or the acyl group can be substituted with a halogen atom, an alkyl group, a cycloalkyl group, an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, a carboxy group or its ester, an alkylcarbonyl group, an arylcarbonyl group, an amino group,

an alkylamino group, an arylamino group, a mercapto group, an alkylthio group, an arylthio group, a cyano group, a nitro group or a heterocycle, and further the alkyl group, the cycloalkyl group, the aryl group, the alkoxy group, the aryloxy group, the alkylcarbonyl group, the arylcarbonyl group, the alkylamino group, the arylamino group, the alkylthio group, the arylthio group or the heterocycle can be substituted with an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, an alkoxyalkoxy group, a carboxy group or its ester;

R^4 and R^5 can be bound to form a heterocycle, the heterocycle can be substituted with a halogen atom, an alkyl group, a cycloalkyl group, an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, a carboxy group or its ester, and further the alkyl group, the cycloalkyl group, the aryl group, the alkoxy group or the aryloxy group can be substituted with an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, an alkoxyalkoxy group, a carboxy group or its ester; and

A_1 represents an alkylene group.

4. The inhibitor of pain threshold decrease as claimed in claim 3, wherein the κ-opioid receptor agonist is

3-acetyl-6-chloro-2-[2-(3-(N-(2-hydroxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline,
3-acetyl-6-chloro-2-[2-(3-(N-(2-methoxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline,
3-acetyl-6-chloro-2-[2-(3-(N-(2-ethoxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline,
or a salt thereof.

5. The inhibitor of pain threshold decrease as claimed in claim 1 or 2, wherein the κ-opioid receptor agonist is an arylacetic acid (N-alkyl-N-(N',N'-dialkyl)aminoalkyl)amide derivative.

6. The inhibitor of pain threshold decrease as claimed in claim 5, wherein the κ-opioid receptor agonist is
trans-2-(3,4-dichlorophenyl)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide,
2,2-diphenyl-N-[2-(3-(S)-hydroxy-1-pyrrolidinyl)-1-(S)-phenylethyl]methylacetamide,
or a salt thereof.

7. The inhibitor of pain threshold decrease as claimed in anyone of claims 1 to 6, characterized in that the κ-opioid receptor agonist is continuously administered.

NAME OF THE DOCUMENT

SPECIFICATION

TITLE OF THE INVENTION

INHIBITOR OF PAIN THRESHOLD DECREASE

[Technical Filed]

[0001]

The present invention relates to an inhibitor of pain threshold decrease comprising a κ-opioid receptor agonist as an active ingredient.

[Background Art]

[0002]

As an opioid receptor, three opioid receptors, μ-, κ- and δ-opioid receptors have been known (Non-patent Literature 1). The μ-opioid receptor is distributed in the cerebral cortex, amygdaloid nucleus and the like, and main agonists are morphine, codeine and the like. The κ-opioid receptor is distributed in the hypothalamus, spinal cord and the like, and its agonists are ketocyclazocine and the like. The δ-opioid receptor is distributed in the extrapyramidal system, and its agonists are enkephalin and the like. The μ-opioid receptor agonist typified by morphine and codeine has an excellent analgesic activity, but its dependence on the body and mind is strong, and it involves side effects such as complication of constipation.

[0003]

Meanwhile, the κ-opioid receptor agonist is characterized in that it does not exhibit dependence unlike morphine, and trans-2-(3,4-dichlorophenyl)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide (U-50488), 2,2-diphenyl-N-[2-(3-(S)-hydroxy-1-pyrrolidinyl)-1-(S)-phenylethyl]methylacetamide (Asimadoline) and the like are known (Non-patent Literature 1, Non-patent Literature 2).

[0004]

Pain is roughly classified into acute pain and chronic pain. The acute pain is pain accompanied by tissue disorders, and causal association with tissue disorders is clear. Meanwhile, the chronic pain is pain which continues even after curing tissue disorders, and no clear organic cause has been found out. However, it has been reported that a plastic change of a descending inhibition system participates in development of the chronic pain (Non-patent Literature 3). When pain is prolonged, a pain threshold is gradually decreased, and pain is felt also due to an action, a tactile sense or the like which has not given a feel of pain. The pain threshold here referred to indicates a sensitivity of pain. More specifically, it indicates the minimum level of pain that is felt when pain is given.

[0005]

Accordingly, the decrease in pain threshold amplifies the pain and entails the chronic pain. Therefore, when the decrease in pain threshold can be inhibited, it is possible to effectively treat the chronic pain. Non-patent Literature 4 reports that neurotropin, an agent for treating chronic pain can inhibit a decrease in pain threshold by activating a descending inhibition system. However, its chronic pain- inhibiting effect is not necessarily satisfactory.

[Non-patent Literature 1] K.K. Mikusu, Opioid no Subete, 25-36 (1999))

[Non-patent Literature 2] K.K. Mikusu, "Opioid no Subete", 213-232 (1999)

[Non-patent Literature 3] K.K. Mikusu, "Opioid Chiryo", 246-253 (2000)

[Non-patnet Literature 4] Japan J. Pharmacol., 57, 243-250 (1991)

[DISCLOSURE OF THE INVENTION]

[Problem to be Solved by the Invention]

[0006]

As stated above, a therapeutic agent effective for treating chronic pain can be provided by searching a drug for inhibiting a decrease in pain threshold.

[Means for Solving the Problem]

[0007]

The present inventors conducted a test for inhibiting a decrease in pain threshold based on repetitive cold stress models on various κ-opioid receptor agonists. They have then found that all of κ-opioid receptor agonists have an excellent activity on inhibiting a decrease in pain threshold. Accordingly, the κ-opioid receptor agonists can radically improve the chronic pain caused by the decrease in pain threshold. The repetitive cold stress model which is one of chronic pain models is based on the fact that a decrease in function of a descending inhibition system induces a decrease in pain threshold.

[0008]

The present invention is an inhibitor of pain threshold decrease comprising a κ-opioid receptor agonist as an active ingredient, and this inhibitor is characterized in that it is greatly effective for treating chronic pain in particular. Further, the present invention is characterized in that the κ-opioid receptor agonist is continuously administered as required to inhibit the decrease in pain threshold.

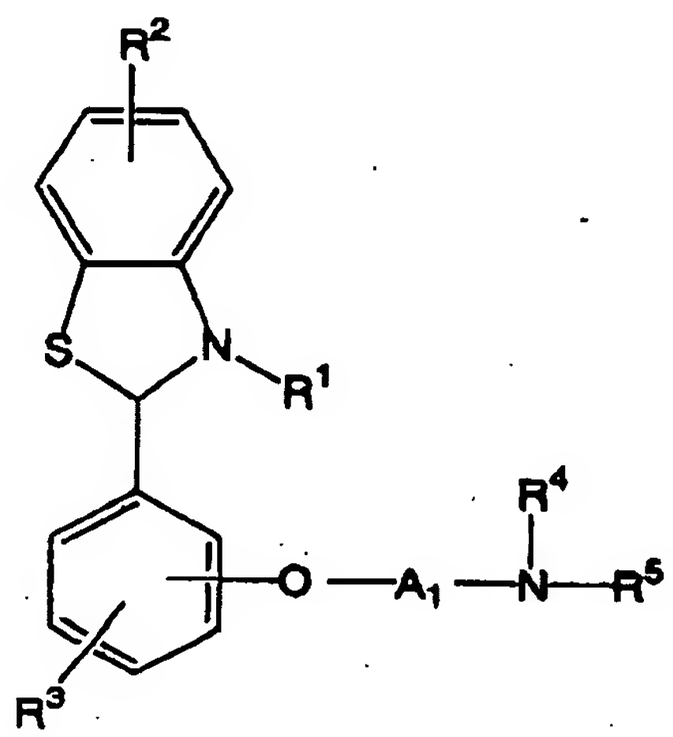
[0009]

The κ-opioid receptor agonist of the invention is not particularly limited, and is exemplified by compounds

described in Japanese Patent Application No. 2002-97500 and arylacetic acid (N-alkyl-N-(N',N'-dialkyl)aminoalkyl)amide derivatives. These κ-opioid receptor agonists have an excellent activity on inhibiting a decrease in pain threshold as will be described in detail under the item "Pharmacological Test".

[0010]

Japanese Patent Application No. 2002-97500 discloses compounds represented by the following formula or salts thereof.



[0011]

wherein R^1 represents an acyl group;

R^2 and R^3, which are the same or different, represent a hydrogen atom, a halogen atom, an alkyl group, a cycloalkyl group, an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, a carboxy group

or its ester, an alkylcarbonyl group, an arylcarbonyl group, an amino group, an alkylamino group, an arylamino group, a cyano group or a nitro group, the alkyl group, the cycloalkyl group, the aryl group, the alkoxy group, the aryloxy group, the alkylcarbonyl group, the arylcarbonyl group, the alkylamino group or the arylamino group can be substituted with a halogen atom, an alkyl group, a cycloalkyl group, an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, a carboxy group or its ester, an alkylcarbonyl group, an arylcarbonyl group, an amino group, an alkylamino group, an arylamino group, a cyano group or a nitro group;

[0012]

R^4 and R^5, which are the same or different, represent a hydrogen atom, an alkyl group, a cycloalkyl group, an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group or an acyl group, the alkyl group, the cycloalkyl group, the aryl group, the alkoxy group, the aryloxy group or the acyl group can be substituted with a halogen atom, an alkyl group, a cycloalkyl group, an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, a carboxy group or its ester, an alkylcarbonyl group, an arylcarbonyl group, an amino group, an alkylamino group, an arylamino group, a mercapto group, an alkylthio group, an arylthio group, a cyano group, a

nitro group or a heterocycle, and further the alkyl group, the cycloalkyl group, the aryl group, the alkoxy group, the aryloxy group, the alkylcarbonyl group, the arylcarbonyl group, the alkylamino group, the arylamino group, the alkylthio group, the arylthio group or the heterocycle can be substituted with an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, an alkoxyalkoxy group, a carboxy group or its ester;

[0013]

R^4 and R^5 can be bound to form a heterocycle, the heterocycle can be substituted with a halogen atom, an alkyl group, a cycloalkyl group, an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, a carboxy group or its ester, and further the alkyl group, the cycloalkyl group, the aryl group, the alkoxy group or the aryloxy group can be substituted with an aryl group, a hydroxyl group or its ester, an alkoxy group, an aryloxy group, an alkoxyalkoxy group, a carboxy group or its ester; and

[0014]

A_1 represents an alkylene group.

[0015]

Examples of the compounds represented by the general formula include

3-acetyl-6-chloro-2-[2-(3-(N-(2-hydroxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl)benzothiazoline,

3-acetyl-6-chloro-2-[2-(3-(N-hydroxy-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline,

3-acetyl-6-chloro-2-[2-(3-(N-isopropyl-N-(2-methoxyethyl)amino)propoxy)-5-methoxyphenyl]benzothiazoline,

3-acetyl-6-chloro-2-[2-(3-(N-(2-ethoxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline,

3-acetyl-5-chloro-2-[2-(3-(N-(2-hydroxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline,

3-acetyl-6-chloro-2-[2-(3-(N-(2-hydroxyethyl)-N-isopropylamino)-1-methylpropoxy)-5-methoxyphenyl]benzothiazoline,

3-acetyl-2-[2-(3-(N-(2-ethoxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline,

3-acetyl-6-chloro-2-[2-(3-(N-(2-methoxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline,

3-acetyl-6-chloro-2-[2-(3-(N-isopropyl-(N-methoxymethyloxyethyl)amino)propoxy)-5-methoxyphenyl]benzothiazoline,

3-acetyl-6-chloro-2-[2-(3-(N-isopropyl-N-(2-(2-methoxyethoxymethoxy)ethyl)amino)propoxy)-5-methoxyphenyl]benzothiazoline,

2-[2-(3-(N-(2-acetoxyethyl)-N-isopropylamino)propoxy)-5-

methoxyphenyl]-3-acetyl-6-chlorobenzothiazoline, 3-acetyl-6-chloro-2-[2-(3-(N-isopropyl-N-phenylcarboxyethylamino)propoxy)-5-methoxyphenyl]benzothiazoline and the like.

Preferred compounds are 3-Acetyl-6-chloro-2-[2-(3-(N-(2-hydroxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline, 3-acetyl-6-chloro-2-[2-(3-(N-(2-methoxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline, 3-acetyl-6-chloro-2-[2-(3-(N-(2-ethoxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline.

[0016]

As arylacetic acid (N-alkyl-N-(N',N'-dialkyl)aminoalkyl)amide derivatives, compounds having a common structure of phenylacetic acid (N-methyl-N-pyrrolidinylethyl)amide or salts thereof described in Non-patent Literature 2 are preferable.

Specific examples of these compounds include U-50488H, PD-117302, Spiradoline, Enadoline, HN-11608, BRL-52537, BRL-52580, BRL-52974, ZT-52656A, GR-89696, GR-94839, GR-45809, GR-91272, GR-129083, R-84760, Niravoline, Dup-747, ICII99441, ICI-204448, EMD60400, Fedotozine, Asimadoline, and the like. U-50488H and Asimadoline are more preferable.

[0017]

The κ-opioid receptor agonist may be the compound

having the chemical structure other than the above. A large number of compounds are disclosed in Non-patent Literature 2, and Tifluadom, Apadoline, TRK-820, HZ-2 are particularly preferable.

[0018]

In the invention, the "salts" are not particularly limited so long as they are pharmaceutically acceptable salts. Examples of salts are salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid and phosphoric acid, salts with organic acids such as acetic acid, fumaric acid, maleic acid, succinic acid, citric acid, tartaric acid, adipic acid, lactic acid, methanesulfonic acid, trifluoromethanesulfonic acid and p-toluenesulfonic acid, salts with alkali metals such as lithium, sodium and potassium, salts with alkaline earth metals such as calcium and magnesium, quaternary salts with ammonia and methyl iodide, and the like. When the compounds represented by the above-mentioned general formula, the compounds having the structure of arylacetic acid (N-alkyl-N-(N',N'-dialkyl)aminoalkyl)amide and the like have geometric isomers or optical isomers, these isomers are also included in the scope of the present invention, and these compounds can be in the form of hydrates or solvates.

[0019]

From the results of a test for inhibition of pain threshold decrease by a repetitive cold stress in the case of single administration, it was revealed that the inhibitor of pain threshold decrease of the present invention sustained the pain threshold increasing activity, and turned out not to be one that temporarily leads to the pain threshold inhibiting activity. Therefore, the inhibitor of pain threshold decrease of the present invention is considered to be one wherein denaturation of the descending inhibition nerve due to prolonged pain is reversibly changed. Accordingly, since the inhibitor of pain threshold decrease of the present invention is not a pharmacological composition for responsive treatment that inhibits pain threshold decrease temporarily, it can radically improve diseases with the decrease in pain threshold.

[0020]

The κ-opioid receptor agonist of the invention can be administered either orally or parenterally. Examples of the dosage form include tablets, capsules, granules, powders, injection solutions, eye drops and the like. These can be prepared by techniques which have been widely used.

[0021]

For example, oral preparations such as tablets, capsules, granules and powders can be prepared using, as required, excipients such as lactose, mannitol, starch, crystalline cellulose, light anhydrous silicic acid, calcium carbonate and calcium hydrogenphosphate, lubricants such as stearic acid, magnesium stearate and talc, binders such as starch, hydroxypropylcellulose, hydroxypropylmethylcellulose and polyvinyl pyrrolidone, disintegrants such as carboxymethylcellulose, low-substituted hydroxypropylcellulose and calcium citrate, coating agents such as hydroxypropylmethylcellulose, macrogol and silicone resin, stabilizers such as ethyl p-oxybenzoate and benzyl alcohol, corrigents such as sweetening agents, sour agents and flavors, and the like.

[0022]

Parenteral preparations such as injection solutions and eye drops can be prepared using, as required, tonicity agents such as sodium chloride and conc. glycerin, buffers such as sodium phosphate and sodium acetate, surfactants such as polyoxyethylenesorbitan monooleate, polyoxy 40 stearate and polyoxyethylene hydrogenated castor oil, stabilizers such as sodium citrate and sodium edetate, preservatives such as benzalkonium chloride and paraben, and the like.

[0023]

The dose of the κ-opioid receptor agonist according to the present invention can properly be selected depending on the condition of a disease, the age of a patient, the dosage form and the like. For example, an oral preparation can be administered at a dose of, usually from 0.1 to 5,000 mg, preferably from 1 to 1,000 mg per day either once or in several portions.

[Advantages of the Invention]

[0024]

As is apparent from the results of a pharmacological test described later, when the κ-opioid receptor agonist is continuously administered, the decrease in pain threshold in the repetitive cold stress can effectively be inhibited. Accordingly, the κ-opioid receptor agonist is useful as an inhibitor of pain threshold decrease, and is effective for treating chronic pain caused by the decrease in pain threshold in particular.

[Best Mode for Carrying out the Invention]

[0025]

Examples of the invention are described below. However, these are for understanding the invention well, and are not to limit the scope of the invention.

[Examples]

[0026]

[Pharmacological Test]

1. Test for inhibition of pain threshold decrease by repetitive cold stress (continuous administration)

It is reported in Int Acad Biomed Drug Res. 11:277-280 (1996) by Hata T. et al. that a pain threshold is decreased by applying a repetitive cold stress to experimental animals. Accordingly, repetitive cold stress models were prepared according to the method described in the foregoing document, and an activity of each test compound on a decrease in pain threshold was evaluated.

[0027]

(Preparation of repetitive cold stress models)

Everyday in the daytime (from 11:00 A.M. to 6:00 P.M.), the position of rats was changed between a breeding room maintained at room temperature (23°C) and a cage put in a cold room set at -3°C every one hour. From evening to morning (from 6:00 P.M. to 9:00 A.M.), rats were bred in a cold room maintained at -3°C.

[0028]

(Pain threshold measurement: Randall-Selitto method)

A pain threshold was measured according to a paw pressure pain method (Randall-Selitto method) that Randall L. O. et al. have reported in Arch. Int. Pharmacodyn. Ther., 111, 409-419 (1957). That is, the right hind paw was gradually pressed with a pressure stimulation analgesic effect device, and a pressure when showing a

squeaking reaction or an escaping reaction was defined as a pain threshold (mmHg).

[0029]

(Preparation of a test compound solution)

The following compounds were used as a κ-opioid receptor agonist;

(+)-3-acetyl-6-chloro-2-[2-(3-(N-(2-hydroxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl]benzothiazoline hydrochloride (compound A),

(+)-3-acetyl-6-chloro-2-[2-(3-(N-(2-methoxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl] benzothiazolinediacetyl tartrate (compound B),

(+)-3-acetyl-6-chloro-2-[2-(3-(N-(2-ethoxyethyl)-N-isopropylamino)propoxy)-5-methoxyphenyl] benzothiazolinediacetyl tartrate (compound C),

2,2-diphenyl-N-[2-(3-(S)-hydroxy-1-pyrrolidinyl)-1-(S)-phenylethyl]methylacetamide hydrochloride (compound D), and trans-2-(3,4-dichlorophenyl)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide (compound E).

Diclofenac (compound F), a typical compound of a non-steroidal antiinflammatory and analgesic drug, was used as a comparative compound,. Each test compound was dissolved in a 1% methylcellulose solution or a 0.9% physiological saline solution to prepare a test compound solution such that a dose was 5 mL per kg of the body

weight.

[0030]

As a control, 1% methylcellulose (solvent alone) was used in an oral administration test, and a 0.9% physiological saline solution was used in a subcutaneous administration test.

[0031]

(Route of administration and dose of a test compound)

Compounds A, B, and C were orally administered at a dose of 3 mg/kg, compound D at a dose of 100 mg/kg, and compound F at a dose of 10 mg/kg respectively. Compound E was subcutaneously administered at a dose of 3 mg/kg.

[0032]

(Test method)

The test compound solution was subjected to intragastric forced oral administration or dorsal subcutaneous administration once a day from the day when the repetitive cold stress was applied. A pain threshold was measured according to the Randall-Selitto method everyday from the day when the stress was applied after rats were bred in an atmosphere of room temperature for approximately 2 hours and before administering the next test compound.

[0033]

(Test results)

Fig. 1 shows a change with time (day 1 after administration of the test compound) of the pain threshold (mmHg) in repetitive cold stress rat models when using each test compound (each of compounds A to D). Table 1 shows a rate of inhibition of pain threshold decrease of each test compound on day 8 after applying the repetitive cold stress. The rate of inhibition of pain threshold decrease (%) was calculated by the following formula using a pain threshold of a solvent administration group as a standard. In Fig. 1 and Table 1, the pain threshold and the rate of inhibition of pain threshold decrease are shown in terms of an average value of 5 or 6 cases.

Rate of inhibition of pain threshold decrease (%) = {1-(pain threshold of solvent administration group 2 - pain threshold of test compound administration group) / (pain threshold of solvent administration group 2 - pain threshold of solvent administration group 1)} x 100

[0034]

Table 1

	Test compound	Stress application	Rate of inhibition of pain threshold decrease (%)
Example 1	Compound A	with	52.1
Example 2	Compound B	with	53.9
Example 3	Compound C	with	73.4
Example 4	Compound D	with	45.0
Example 5	Compound E	with	59.6
Comparative Example 1	Compound F	with	2.0
Solvent administration group 1	-	with	0.0
Solvent administration group 2	-	without	100

[0035]

(Consideration)

As is apparent from Fig. 1, in solvent administration group 1, when the repetitive cold stress was applied to rats, the notable decrease in pain threshold was observed for five days after stress application followed by flat state. The κ-opioid receptor agonists (Examples 1 to 5) inhibit the decrease in pain threshold, whereas with diclofenac (Comparative Example 1), a non-steroidal antiinflammatory drug, an activity on inhibiting a pain threshold was not observed at all. As is clear from Table 1, the rate of inhibition of pain threshold decrease in the κ-opioid receptor agonists

(Examples 1 to 5) was from 45 to 73%, whereas an activity on inhibiting a decrease in pain threshold was not observed at all in diclofenac.

[0036]

2. Test for inhibition of pain threshold decrease by repetitive cold stress (single administration)

The test was conducted in the same manner as the foregoing "1. Test for inhibition of pain threshold decrease by repetitive cold stress (continuous administration)" except that each test compound (each of compounds A to D) was administered once after 8 days from the day when the repetitive cold stress was applied, and a pain threshold after 24 hours from the administration of each test compound was measured.

[0037]

[Test results]

Table 2 shows a pain threshold (mmHg) and a rate of inhibition of pain threshold decrease when 24 hours elapsed after administering each test compound on day 8 from applying of the repetitive cold stress. The pain threshold and the rate of inhibition of pain threshold decrease in Table 2 are shown in terms of an average value of 6 cases.

Table 2

	Test compound	Stress application	Pain threshold (mmHg)	Rate of inhibition of pain threshold decrease (%)
Example 6	Compound A	with	21.7	0
Example 7	Compound B	with	21.5	-1.9
Example 8	Compound C	with	21.7	0
Example 9	Compound D	with	21.5	-1.9
Solvent administration group 3	-	with	21.7	0
Solvent administration group 4	-	without	30.7	100

[0038]

(Consideration)

As shown in Table 2, the decrease in pain threshold was clearly observed in rats with the stress applied for 8 days in comparison with rats without the stress application. When the κ-opioid receptor agonist was administered to rats with the stress applied, the pain threshold when 24 hours elapsed after administration was not found to be different from the pain threshold of the solvent administration group.

[0039]

[Preparation Example]

A general preparation example of the inhibitor of pain threshold decrease in the invention is described below.

[0040]

1) Tablets

Formulation 1	In 100 mg,	
Compound A		1 mg
Lactose		66.4 mg
Cornstarch		20 mg
Calcium carboxymethylcellulose		6 mg
Hydroxypropylcellulose		4 mg
Magnesium stearate		0.6 mg

[0041]

The tablets of the foregoing formulation were coated with 2 mg of a coating agent (a usual coating agent such as hydroxypropylmethylcellulose, macrogol or a silicone resin) to obtain desired coated tablets. Desired tablets can be obtained by properly changing the amounts of compound A and additives.

[0042]

2) Capsules

Formulation 1	In 150 mg,	
Compound B		5 mg
Lactose		145 mg

[0043]

Desired capsules can be obtained by properly changing the mixing ratio of compound B and lactose.

[Brief Description of the Drawing]

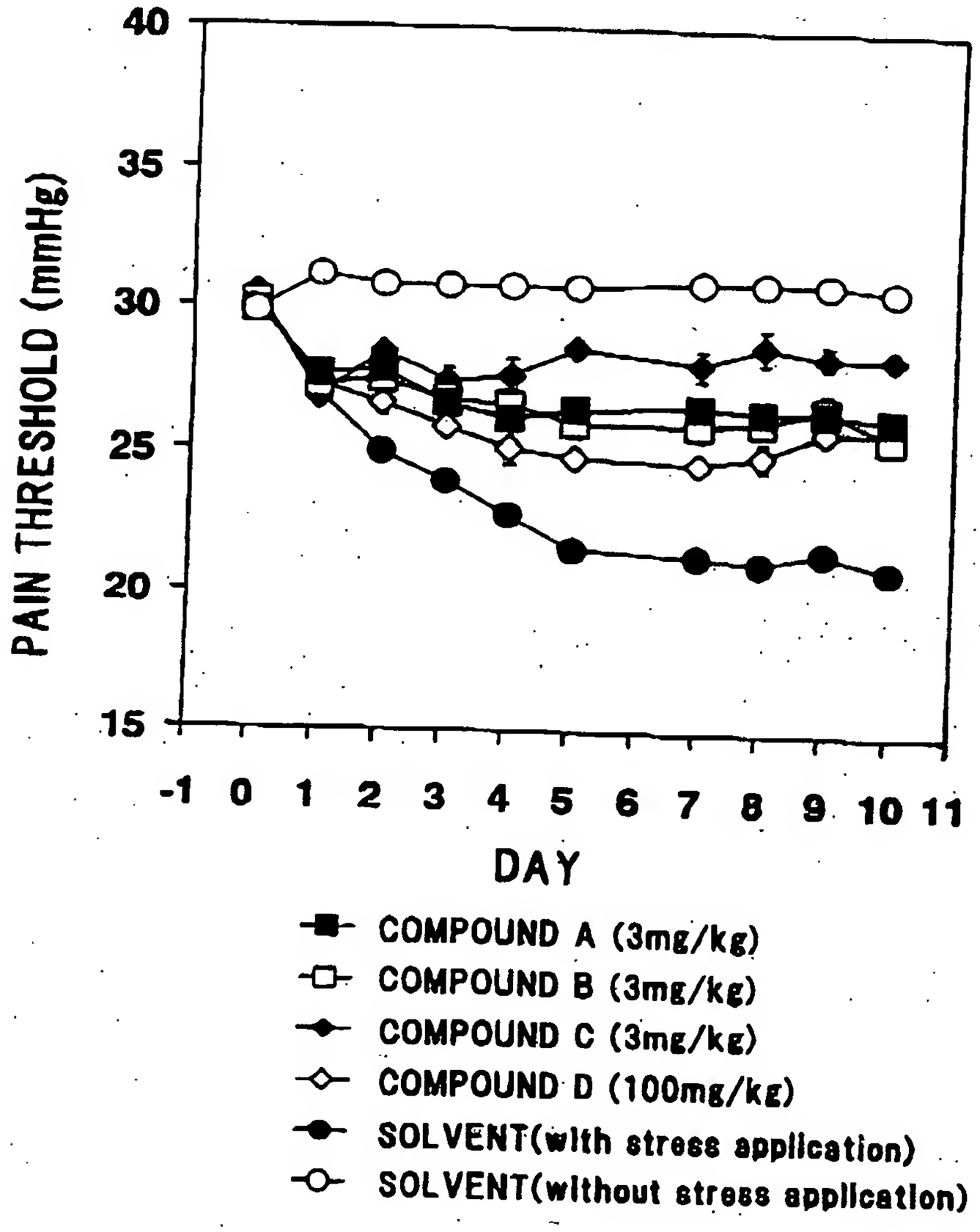
[0044]

Fig. 1 is a graph showing a change with time of a pain threshold (mmHg) in repetitive cold stress rat models when using test compounds.

NAME OF THE DOCUMENT

DRAWINGS

Fig. 1



NAME OF THE DOCUMENT

ABSTRACT

[Abstract]

[Object]

To search a drug having an activity on inhibiting a decrease in pain threshold.

[Means for Fulfilling the Object]

Since a κ-opioid receptor agonist effectively inhibits the decrease in pain threshold, it is useful as an inhibitor of pain threshold decrease.

[Selected Drawing]

None